08/418870

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/418,870	04/07/95	VAN NEST	G 0085.006

EXAMINER

HM21/0527

BARBARA G MCCLUNG
CHIRON CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT R440
P O BOX 8097
EMERYVILLE CA 94662-8097

WORTMAN, D

ART UNIT	PAPER NUMBER
1643	45

DATE MAILED: 05/27/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 1/20/98

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-9, 29, 36, 37 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-9, 29, 36, 37 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 42
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1643.

Claim 1 was amended and new claim 37 was added in Paper No. 44. Claims 1-9, 29, 36 and 37 are pending.

Rejections made in the previous Office action under 35 U.S.C. 102(b) over Idson and under 35 U.S.C. 102(b) over US Patent No. 4,647,586 to Mizushima et al. are withdrawn in view of Applicant's amendment to claim 1.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 29 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoskinson et al. and Glass et al. in view of Idson and Remington for reasons of record in Paper No. 38.

Applicant has argued 1) that, with respect to the Declaration submitted as part of Paper No. 40, the showings of the Declaration were provided in rebuttal to the previous Examiner's assertion that applicant's compositions are likely to act in the same manner as the compositions of Glass with respect to depot effects, and therefore the Declaration tends to bolster applicants' assertions that the Glass

compositions are not analogous to applicants'. Applicant further argues 2) that the Glass compositions have a synthetic matrix that binds or traps the antigen and results in slow release of antigen; 3) that the Glass compositions are highly viscous formulations; 4) that rapid dispersibility and low viscosity are inherent properties of applicants' compositions by virtue of the combination of elements, including particle size; 5) that one of skill in the art would not be motivated to alter the Glass compositions in order to obtain applicants' composition. Applicant has 6) pointed to locations in the specification where reference to 'MF59' appears. Applicant has argued 7) that Hoskinson teaches away from the use of oil-in-water emulsions and pointed to column 3, lines 22-24, in support. Applicant has argued 8) that Idson and Remington disclose known adjuvants and summarize known physical properties of emulsions and 9) do not suggest that the formulations of Hoskinson and Glass could be modified to give the instant compositions. Applicant has 10) reviewed the criteria for *prima facie* obviousness, including the criterion that the prior art references must teach or suggest all of the claim limitations, and asserted that the Office has failed to satisfy the criteria. Applicant has 11) asserted that improper hindsight has been applied.

These arguments have been considered but not found persuasive for the following reasons. With respect to all the numbered points, insofar as they are all directed toward distinguishing over the prior art compositions, Applicant has relied upon limitations not found in the claims; the use of the open language "comprising" does not preclude the addition of other items except for the specifically excluded block

copolymer and muramyl peptide. It is noted that if claim 1 were to be amended to recite "consisting essentially of" in place of "comprising"; and if claim 37 were to be rewritten in independent form to recite, e.g.:

"An adjuvant composition consisting essentially of:

(1) a metabolizable oil;

(2) an emulsifying agent, wherein said oil and said emulsifying agent are present in the form of an oil-in-water emulsion having oil droplets substantially all of which are less than 1 micron in diameter and wherein said composition exists in the absence of any polyoxypropylene block copolymer and in the absence of any muramyl peptide, and further wherein said adjuvant composition is capable of increasing the immune response to an antigen when administered with the antigen; and

(3) a selected antigen.",

claims written in such a manner would be deemed to distinguish over Glass and Hoskinson, and the rejection under 35 U.S.C. 103(a) as being unpatentable over Hoskinson et al. and Glass et al. in view of Idson and Remington would be withdrawn.

With respect to point 6), it is agreed that the specification makes reference to 'MF59' as a composition of the instant invention; however, it is noted it is not possible to determine the exact ingredients and proportions of ingredients that make up 'MF59' based solely on the specification which makes mention at page 58, line 31, of "MF69 and MF59, differing only in the Tween 80:Span 85 ratio ...". Further, there is some inconsistency in terminology within the

specification and between the Declaration and the specification, since in the specification at pages 58-59, MF59 plus MTP-PE is referred to as an "MF59 formulation"; at the bottom of page 59, "MF59 but with MTP-PE added exogenously" is referred to as "MF58". The Declaration refers to MF59 as being a particular composition consisting of squalene and emulsifying agents ("composition having 5% squalene (v/v), 0.5% polysorbitan 80, 0.5% sorbitan trioleate"). If Applicant wishes to rely upon the contents of the Declaration to further distinguish over the art of record, these apparent inconsistencies need to be addressed; at minimum, Applicant is requested to provide evidence on the record that the MF59 of the Declaration is the same composition as the MF59 referred to in the specification, since it is not possible to discern the exact formulation of MF59 from the specification. With respect to point 11), it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Knowledge of adjuvants comprising oil-in-water emulsions as claimed was clearly available at the time of Applicant's invention, as evidenced by the prior art of record.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art

> are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 29 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodard et al., Vaccine 3:137-144, 1985, in view of Silvestri et al., both cited by Applicant on PTO 1449 submitted as Paper No. 42 on January 20, 1998. Woodard discloses an adjuvant composition comprising a metabolizable oil (hexadecane, as exemplified, or, alternatively, soybean or peanut oil, squalene, and squalane are also disclosed as metabolizable oils) and an emulsifying agent (a polyoxyethylene sorbitan mono-, di- or trioleate or a sorbitan mono-, di-, or triester) as an oil-in-water emulsion. These compositions exist in the absence of a polyoxypropylene-polyoxyethylene block copolymer and in the absence of any muramyl peptide. While Woodard does not specifically disclose that "substantially all" of the droplets are less than 1 micron in diameter, insofar as can be ascertained from the copy of Fig. 1 provided, Woodard's droplets appear to be much smaller than the 2.5 μm calibration line in Fig. 1(a); further, Woodard discloses that small droplet size is a desirable feature of a stable emulsion and so one would have been motivated to use an emulsion with droplet size as small as possible in order to obtain a stable composition. Silvestri et al. disclose the desirability of small, in particular, submicron size droplets for achieving improved stability in oil-in-water emulsions and disclose a device and method for achieving such submicron droplets. Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to have made and used an adjuvant composition comprising a metabolizable oil and an emulsifying agent

wherein said oil and said emulsifying agent are present in the form of an oil-in-water emulsion having oil droplets substantially all of which are less than 1 micron in diameter, wherein the composition exists in the absence of block copolymer and muramyl peptide, because of Woodard's disclosure of such an adjuvant composition, the teachings of both Woodard and Silvestri that smaller droplet size is desirable for oil-in-water emulsions in order to obtain the advantage of improved stability, and the teaching of Silvestri that submicron droplets are both desirable and achievable.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on January 20, 1998, prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee of $790 for a large entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. If a notice of appeal and the appeal fee set forth in 37 CFR 1.17(e) were filed prior to or with the payment of the fee set forth in 37 CFR 1.17(r), the payment of the fee set forth in 37 CFR 1.17(r) by applicant will be construed as a request to dismiss the appeal and to continue prosecution under 37 CFR 1.129(a). In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Wortman whose telephone number is (703) 308-1032. The examiner can normally be reached on Monday through Thursday from 7:30 am to 5:00 pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Donna C. Wortman, Ph.D.
Patent Examiner

May 24, 1998